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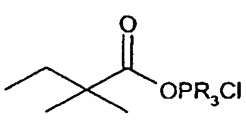
(54) Title: A PROCESS FOR PRODUCING SIMVASTATIN



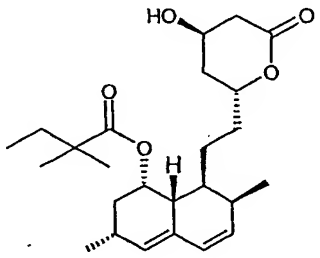
(VI)

(57) Abstract: The present invention relates to a process for producing Simvastatin comprising the steps of acylating 6(R)-[2-(8'(S)-hydroxy-2'(S),6'(R)-dimethyl-1',2',6',7',8',8'a(R)-hexahydronaphthyl-1'(S)ethyl-4(R)-t-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-on with the carboxylic acid compound of formula (VI) wherein R is methyl, ethyl, propyl, n-butyl, t-butyl or phenyl, and hydroxylating the resulting compound.

A PROCESS FOR PRODUCING SIMVASTATIN

FIELD OF THE INVENTION

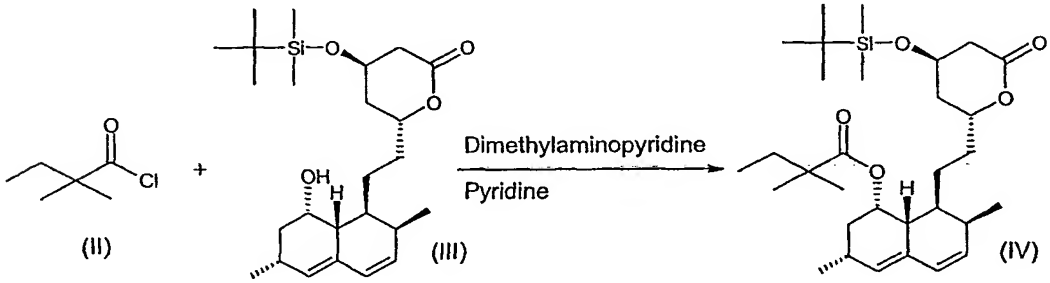
The present invention relates to a process for producing the Simvastatin compound. This compound has the following formula I:



(I)

and is useful in inhibiting the biosynthesis of cholesterol.

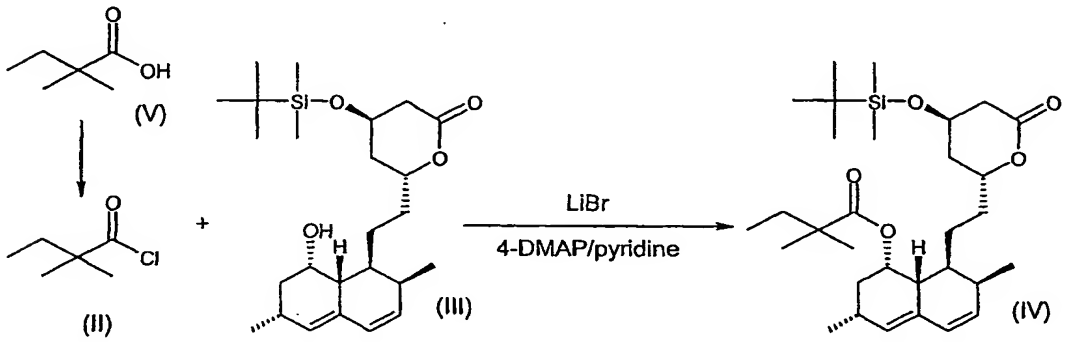
It is known that the Simvastatin compound is a suppressor of HMG CoA reductase and is a medicament useful for the treatment of hypercholesterolemia. Several processes for producing said compound are disclosed. One is disclosed in US Patent No. 4,444,784 (corresponding to Korean Publication Patent No. 85-669) with the following reaction mechanism:



DESCRIPTION OF THE PRIOR ART

The said process described in US Patent No. 4,444,784 is generally performed in the presence of an excess acylchloride (II) under the condition of high temperature and a long reaction time. In addition, said process has the following disadvantages: i) lower yield of acylated substance; ii) production of by-product due to removal of t-butyldimethylsilyloxy radical; and iii) difficulty separating the resulting substance, ester (IV), from the residual alcohol (III) and acylchloride (II). The residual substances may inhibit the crystallization of the resulting substance.

A process for reforming the above-mentioned process is described in US Patent No. 4,845,237. Its reaction mechanism is as follows:



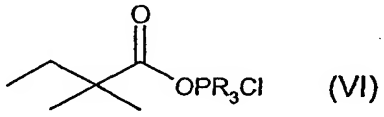
This process reduces the production of by-product and increases the yield of resulting substances by activating acylchloride (II) through the addition of alkalic metal and 4-dialkylaminopyridine. However, this process is also troublesome in that acylchloride (II) should be prepared from carboxylic acid (V), and the LiBr involved in activation of acylchloride is a substance the treatment of which is very difficult. Using LiBr requires that it be dried at 135°C for 3 days under a vacuum condition. When the dried LiBr is added to acylchloride, it should be treated using plastic container because it is very water-absorbent. If the wetted LiBr is added, the yield is lowered and by-product is produced. Therefore, the process becomes complicated and difficult.

Accordingly, we have researched and developed a new process, which exhibits improved yield by the direct use of carboxylic acid (V) without via

acylchloride (II), and with the use of LiBr.

DETAILED DESCRIPTION OF THE INVENTION

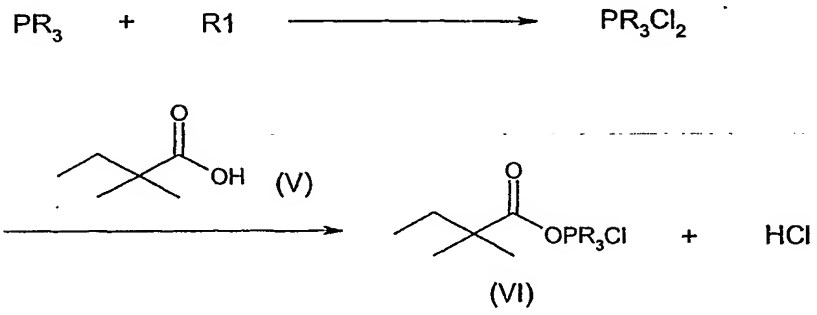
The present invention provides a process for producing Simvastatin comprising the steps of acylating of 6(R)-[2-(8'(s)-hydroxy-2'(s), 6'(R)-dimethyl-1', 2', 6', 7', 8', 8'a(R)-hexahydronaphthyl-1'(S) ethyl-4(R)-t-butylmethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-on with a carboxylic acid compound (VI), and hydroxylating acylated compound. The said carboxylic acid compound has the following formula (VI):



(VI)

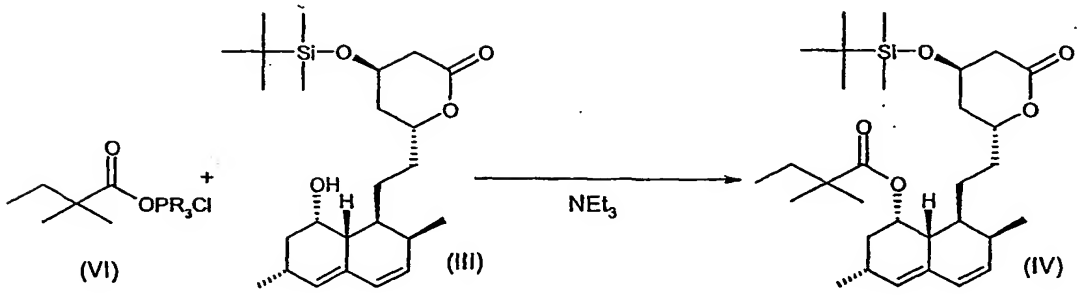
wherein, R is methyl, ethyl, propyl, n-butyl, t-butyl, or phenyl.

In the present invention, carboxylic acid (VI) used for acylation is activated by trialkylphosphine and halogen compounds, and is directly used without separation, which allows for the simplification of the process. This reaction mechanism is as follows:



wherein, R is methyl, ethyl, propyl, n-butyl, t-butyl, or phenyl, R1 is a halogen compound, such as hexachloroethane, carbon tetrachloride, carbon tetrabromide, or hexachloroacetone. When activated carboxylic acid (VI), which is not separated or

purified, reacts with alchol (III), a higher yield of acylated substance (IV) is obtained.



The formula (III) compound of the invention is easily prepared by those skilled in the art. It is preferable that PR_3 of the initial compound (VI) is triphenylphosphine. The halogen compound is preferably hexachloroethane. It may be used in amount of from 1.0 to 4.0 equivalent, preferably from 3.0 to 3.6 equivalent. Temperature is from 0°C to 110°C, preferably 83°C.

The solvent is used alone or in combination with inert solvents, including acetonitrile, dichloromethane, dichloroethane, cyclohexane, and toluene, most preferably dichloroethane.

It is to be understood that the examples which follow, are intended to illustrate and not limit the scope of the invention.

EXAMPLES

Example 1

6(R)-[2-(8'(S)-(4-butyl-2,2-dimethyloxy)-2'(S), 6'(R)-dimethyl-1', 2', 6', 7', 8', 8'a(R)-hexahydronaphthyl-1'(S)ethyl-4(R)-t-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-on

After dissolving 18.1 g of triphenylphosphine into 100 ml of dichloroethane solution, 19.6 g of hexachloroethane was mixed. This solution was stirred at 20°C for 1 hr. 8.0 g of 2,2-dimethylbutylic acid was added to a solution, and the resulting solution was stirred for 45 min. After stirring, 10 g of 6(R)-[2-(8'(S)-hydroxy-2'(S), 6'(R)-dimethyl-1', 2', 6', 7', 8', 8'a(R)-hexahydronaphthyl-1'(S)ethyl-4(R)-t-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-on was added to the solution, and this solution was mildly agitated for 20 hr. As a result of monitoring with HPLC, the conversion rate of the initial substance was 99% or more, and the content ratio of desirable substance (III) and by-product, such as unsaturated lactone, was 96 - 97% and 1 - 2%, respectively. After the conversion was completed, the solution was cooled to 10°C, and 100 ml of 2% hydrochloride was mixed. The resulting solution was stirred and the organic layer was separated. The reaction solution was condensed, and triphenyloxide was crystallized by mixing with 100 ml of cyclohexane. The solution containing crystal was cooled to 10°C, stirred for 2 hr, filtered, and then washed with cooled cyclohexane to obtain the title compound.

Example 2

6(R)-[2-(8'(S)-(4-butyl-2,2-dimethyloxy)-2'(S), 6'(R)-dimethyl-1', 2', 6', 7', 8', 8'a(R)-hexahydronaphthyl-1'(S)ethyl-4(R)-t-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-on

After dissolving 18.1 g of triphenylphosphine into 50 ml of dichloroethane solution, 19.6 g of hexachloroethane was mixed. This solution was added dropwise to the solution with 8.0 g of 2,2-dimethylbutylic acid being added to 50 ml of dichloroethane. The resulting solution was stirred for 1 hr. After stirring, 10 g of 6(R)-[2-(8'(S)-hydroxy-2'(S), 6'(R)-dimethyl-1', 2', 6', 7', 8', 8'a(R)-hexahydronaphthyl-1'(S)ethyl-4(R)-t-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-on was added to the solution, and this solution was mildly agitated for 20 hr. The solution was cooled to 10°C, and 100 ml of 2% hydrochloride was mixed. The resulting solution was stirred and the organic layer was separated. The solution was cooled to 10°C, stirred for 2 hr, filtered, and then washed with cooled cyclohexane to obtain the title compound.

Example 3

Production of Simvastatin

120 ml of acetonitrile was added to a concentrated solution of 6(R)-[2-(8'(S)-(4-butyl-2,2-dimethyloxy)-2'(S), 6'(R)-dimethyl-1', 2', 6', 7', 8', 8'a(R)-hexahydronaphthyl-1'(S)ethyl-4(R)-t-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-on obtained by example 1 or 2. Seven ml of distilled water and 0.5 ml of methanesulfonic acid were added to the solution. This solution was stirred at 50°C for 3 hr. After stirring, 42 ml of 2N NaOH was added to the solution, and the resulting solution was stirred. 150 ml of Ethyl acetate and 150 ml of distilled water were added to a solution, stirred, and the aqueous layer was separated. The organic layer was separated by acidifying the aqueous layer mixed with 125 ml of ethyl acetate using hydrochloride, and concentrated. The concentrate was mixed with 150 ml of toluene and mildly stirred for 3 hr. Toluene was concentrated and separated with the column (the ratio of ethyl acetate to n-hexane is 1 to 1). As a result, 7.7 g of 99.0% or more Simvastatin was obtained.

Example 4

Production of Simvastatin

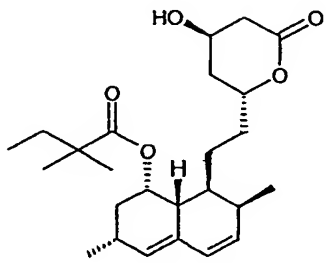
120 ml of acetonitrile was added to the concentrated solution of 6(R)-[2-(8'(S)-(4-butyl-2,2-dimethyloxy)-2'(S), 6'(R)-dimethyl-1', 2', 6', 7', 8', 8'a(R)-hexahydronaphthyl-1'(S)ethyl-4(R)-t-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-on. 7 ml of distilled water and 0.5 ml of methanesulfonic acid were added to the solution. This solution was stirred at 50°C for 3 hr. After stirring, 42 ml of 2N NaOH was added to the solution. 150 ml of Ethyl acetate and 150 ml of distilled water were added to the solution, stirred, and the aqueous layer was separated. The organic layer was separated by acidifying the aqueous layer mixed with 125 ml of ethyl acetate using hydrochloride. 42 ml of methanol and 3.5 ml of 28% ammonia water was added to the organic layer, which leads to crystalization. Crystals were filtered, washed with 20 ml of ethyl acetate/methanol(3.5/1) and 20 ml of toluene, sequentially.

After washing, crystals were added to 150 ml of toluene. Toluene was concentrated and separated. The resulting solution was mixed with 150 ml of cyclohexane, and stirred . As a result, 6.6 g of crude Simvastatin was obtained. The crude Simvastatin was re-crystalized with ethanol/distilled water, and 6.2 g of 90.0% or more Simvastatin was obtained.

It is clear that the present invention is useful in industry because a higher yield of acylated substances (IV) is obtained without use of LiBr and separation of acylchloride (II).

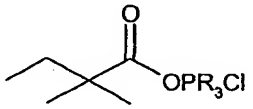
WHAT IS CLAIMS IS:

1. A process for producing the compound of formula (I):



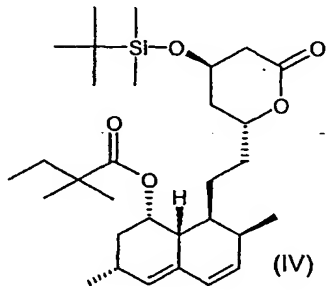
(I)

comprising the steps of reacting 6(R)-[2-(8'(S)-hydroxy-2'(S), 6'(R)-dimethyl-1', 2', 6', 7', 8', 8'a(R)-hexahydronaphthyl-1'(S)ethyl-4(R)-t-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-on with the compound of formula (VI):



(VI)

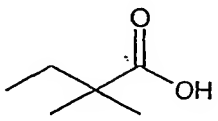
wherein R is methyl, ethyl, propyl, n-butyl, t-butyl, or phenyl; and hydroxylating the resulting compound of formula (IV):



(IV)

2. A process according to claim 1 wherein said compound of formula (VI) is produced by the reaction of halogenide, resulting from the reaction of trialkylphosphine and a halogen compound, with a carboxylic acid compound of

formula (V) and compound of formula (I):



(V)

3. A process according to claim 2 wherein said trialkylphosphine is triphenylphosphine.

4. A process according to claim 2 wherein said halogen compound is hexachloroethane.

5. A process according to claim 2 wherein the amount of halogen compound is from 1.0 to 4.0 equivalent.

6. A process according to claim 1 wherein the organic solvent is dichloroethane.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR00/00283

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 309/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

IPC7 C07D

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Korean Patents ans applications for inventions since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)

MEDLINE(on web), CA(STN),

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5393893 A (APOTEX, INC.) 28 FEB. 1995 ABSTRACT, CLAIMS	1-6
A	EP 0511867 B (MERCK & CO., INC.) 04 NOV. 1992 SCHEME 1, CLAIMS	1-6
A	SARTOR G 'Simvastatin treatment of hypercholesterolemia in patients with insulin dependent diabestes mellitus' INT.J.CLI. PHARMACOL. THER., 1995, Vol.33, No.1, 3-6 ABSTRACT	1-6
&	KR 2000-21998 A (CHEIL JEDANG CO.) 25 APRIL 2000 SEE THE WHOLE DOCUMENT	1-6

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 DECEMBER 2000 (28.12.2000)	29 DECEMBER 2000 (29.12.2000)

Name and mailing address of the ISA/KR	Authorized officer
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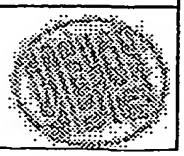

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/00/00283

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5393893 A	28. 02. 1995	WO 95/13283 A	18. 05. 1995
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EP 511867 B	04. 11. 1992	US 5159104 A	27. 10. 1992
		JP 07-64837 B	12. 07. 1995
		DE 69212884 C	26. 09. 1992